specification by the present amendment. The attached page is captioned "**Version with markings to show changes made**."

Rejection under 35 U.S.C. §112

Claims 1-14 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly being indefinite for the recitation of the term "bioequivalents." Applicants respectfully disagree with the Office Action. As the Office Action appears to acknowledge, the specification states on page 8, lines 3-5 that:

> Bioequivalents of oligonucleotides and other nucleic acids are also contemplated such as, but not limited to, oligonucleotide prodrugs, deletion derivatives, conjugates and salts."

The Office Action asserts that Applicants have described "neither structure nor function" of "bioequivalents. However, Applicants assert that those of skill in the art, reading the specification as a whole, and particularly the pasage quoted above, would understand the term "bioequivalent" to denote those species that function as oligonucleotides in an organism (such as oligonucleotide conjugates an salts), or are converted to an oligonucleotide or an active form of an oligonucleotide upon administration to an organism (i.e., oliognucleotide prodrugs). Clearly, the present specification enables the claims in regard to such species. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection under 35 U.S.C. §102

Claims 1-5, 7-12 and 14 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 6,258,600 to Zhang *et al.* (the "Zhang patent"). Applicants do not concur. The present claims recite bi-phasic or multiphasic formulations comprising an oligonucleotide having one or more phosphorothioate linkages and a water-soluble antioxidant, and methods of preventing desulfurization of an oligonucleotide using the claimed formulations. The Zhang patent does not anticipate the claims of the present application, as one of ordinary skill in the art would have to engage in impermissible "picking, choosing and combining" of the elements disclosed in the patent to produce any claimed invention.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987); *MPEP* § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); *MPEP* § 2131. In addition, to anticipate, a reference must "clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without any need for picking, choosing and combining various disclosures not directly related to each other by the teachings of the cited reference." *Akzo v. U.S.I.T.C.*, 808 F.2d 1471, 1480 (Fed. Cir. 1986) (citing *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972)); *In re Schaumann*, 572 F.2d 312, 314 (C.C.P.A. 1978) ("By having to select [a varible] from among the many possibilities which R in the structural formula [of the reference] may be, . . . does not give rise to the claimed compound being fully anticipated by the reference.").

Significantly, the claimed invention can be discerned in the Zhang patent – if at all – only by engaging in the "picking, choosing and combining" that the courts specifically proscribe. The disclosure of the Zhang patent describes a variety of modifications to the oligonucleotide (*e.g.*, backbone modifications, substituted sugar moieties, substituted base modifications, etc.), a substantial number of different modes of administration (*e.g.*, topical, inhalation, oral, parenteral, etc.) as well as a vast number of different formulations (*e.g.*, transdermal patches, ointments, lotions, etc.). Indeed, the discussion of emulsions alone sets forth a number of ingredients, including both oil and water soluble antioxidants, such that one of ordinary skill in the art would have had, at most, very long odds of selecting a combination of elements that falls within the scope of the present claims. (*see* Col. 13, line 55 through Col. 15, line 42). Given the breadth of the disclosure provided by the Zhang patent, and the lack of any specific teaching that water-soluble antioxidants are advantageous, it cannot be said to "clearly and unequivocally disclose the claimed invention." *Akzo*, 808 F.2d at 1480. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections under 35 U.S.C. § 103

Claims 1-14 stand rejected under 35 U.S.C. §103 as allegedly being unpatentable over U.S. Patent No. 6,017,545 to Modi *et al.* (the "Modi patent"), taken in view of the Zhang patent, U.S. Patent No. 5,801,154 to Baracchini *et al.* (the "Baracchinin patent") and U.S. Patent No. 5,525,621 to Burt *et al.* (the "Burt patent"). Applicants respectfully disagree, and assert that it would ***not*** have been obvious to one of ordinary skill in the art

at the time the application was filed to combine or modify the disclosures of the cited references in order to produce a claimed invention.

The Modi patent discusses mixed micellar pharmaceutical formulations and the addition of an antioxidant. Several antioxidants are discussed, however, the Modi patent expressly states that "a preferred antioxidant is tocopherol." (Col. 4, line 52). As set forth above, the present application demonstrates that desulfurization of phosphorothioate oligonucleotides can be prevented by using water-soluble antioxidants. The Modi patent neither discloses or suggests that such a benefit may be derived from employing water-soluble antioxidants. Indeed, the Modi patent ***teaches away*** from such a disclosure by emphasizing the preferred embodiment is an oil-soluble antioxidant, specifically, tocopherol.

The deficiencies of the Modi patent are not remedied by the Burt patent, as there is no disclosure or suggestion therein of the significance of using water-soluble antioxidants as opposed to oil-soluble antioxidants. In addition, pursuant to MPEP § 706.02(k)(E), neither the Zhang nor the Baracchini patents is available as a prior art reference under 35 U.S.C. §103, as each patent and the present application were, "at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." The Zhang and Baracchini patents constitute prior art under 35 U.S.C. §102(e). When such a prior art reference is used in the context of a rejection under section 103, however, the reference may be removed by showing that the "prior art and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person." *MPEP* §706.02(k)(E). At the time the invention was made, the present application and the

Zhang and Baracchini patents were under an obligation of assignment to Isis Pharmaceuticals, Inc. Accordingly, the Zhang and Baracchini references do not constitute proper prior art references for purposes of the rejection under section 103.

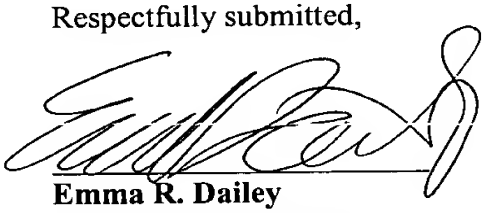
The present application, moreover, discloses unexpected results with respect to the use of certain antioxidants to inhibit desulfurization of an oligonucleotide comprising phosphorothioate linkages. A comparison of the effectiveness of oil-soluble and water-soluble antioxidants indicated that water-soluble antioxidants provide substantial protection from desulfurization in a bi-phasic cream formulation, whereas oil-soluble antioxidants (*e.g.*, BHT, vitamin E and BHA) do not provide such protection. Specifically, Table 3 of Example 4 reports 89.6% to 95.5% of phosphorothioate oligonucleotide present in the bi-phasic cream with water-soluble antioxidants, whereas only 77.3% to 84.8% were present in the same composition with oil-soluble antioxidants. Clearly, this data evinces a surprising result which is neither disclosed nor suggested in the cite references.

Applicants respectfully request reconsideration and withdrawal of the rejection under section 103, as the Modi patent does not disclose or suggest formulations having water-soluble antioxidants to prevent desulfurization of oligonucleotides with one or more phosphorothioate linkages or methods of preventing desulfurization of phosphorothioate oligonucleotides using water-soluble antioxidants. Furthermore, Applicants have provided evidence of surprising results from using water-soluble antioxidants to prevent desulfurization of phosphorothioate oligonucleotides. The deficiencies of the Modi patent cannot be remedied by the Zhang or Baracchini patents, as they have been removed pursuant to *MPEP* §706.02(k)(E). Finally, the Burt patent

does not remedy the deficiencies of the Modi patent, as it does not disclose or suggest the advantage of using water-soluble antioxidants.

All claims are believed to be in condition for allowance. Applicants would like to thank the Examiner for the indication that upon entry of the foregoing amendments, the application would be in condition for allowance. An early Notice of Allowability is, therefore, earnestly solicited.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please amend claims 1, 6, 8 and 13 as follows:

1 (amended). A bi-phasic or multiphasic formulation comprising an oligonucleotide or bioequivalent thereof, [said oligonucleotide comprising] having one or more phosphorothioate linkages, and [an antioxidant which partitions into the aqueous phase of said formulation] a water-soluble antioxidant.

6. The formulation of claim 1, wherein said antioxidant is [selected from the group consisting of] cysteine, glutathione, [a] α -lipoic acid, a 2-mercapto-5-benzimidazole salt [and] or a 2-mercaptoethanesulfonic acid salt.

8 (amended). A method of preventing desulfurization of an oligonucleotide or bioequivalent thereof comprising combining an oligonucleotide having one or more phosphorothioate linkages with a water-soluble antioxidant in a bi-phasic or multi-phasic formulation [, comprising including in said formulation an antioxidant which partitions into the aqueous phase of said formulation].

13 (amended). The method of claim 8, wherein said antioxidant is [selected from the group consisting of] cysteine, glutathione, [a] α -lipoic acid, a 2-mercapto-5-benzimidazole salt [and] or a 2-mercaptoethanesulfonic acid salt.